

Pediatric liquid medicaments – Are they cariogenic?

An *in vitro* study

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Abstract

Aim: Young and chronically sick children receive a variety of oral liquid medications on a routine and regular basis. These pharmaceutical preparations are cariogenic and acidogenic in nature. Hence, the present study was taken up to determine the cariogenic potential of the commonly prescribed pediatric liquid medicaments. **Materials and Methods:** Eight commonly used pediatric liquid medicaments (PLM) were selected and their endogenous pH was measured using a pH electrode meter. The sugar content in them was estimated using High Performance Liquid Chromatography (HPLC). The effect of PLM on *Streptococcus mutans* was assessed by the ditch plate method. **Results:** The pH of the liquid medicaments ranged between 6.05 (Salbid®) and 7.71 (Theopid®). Sucrose was observed in 7 PLM and glucose in 5 PLM. The highest concentration of sucrose was seen in Crocin®. The lowest concentration of sucrose was seen with Althrocin®. Both the antibiotic PLMs inhibited the *S. mutans* growth. Zevit® promoted the growth of *S. mutans*. **Conclusion:** The pH and concentration of sugars of pediatric liquid medicaments can pose as a threat to dental health, especially in chronically sick children, who are on long-term medications.

Key words: Cariogenic potential, drug evaluation, hydrogen ion concentration, pediatric liquid medicaments, pH, *Streptococcus mutans*, *S. mutans* growth, sugar

INTRODUCTION

Pediatric liquid medicaments (PLM) have a long history of use in the field of medicine. They are very commonly prescribed, widely available, and are easily accepted by both parents and children. Young and chronically sick children with cardiac disease,^[1] leukemia,^[2] epilepsy, cystic fibrosis, renal disease, and asthma^[3] are the significant groups of children receiving a variety of oral liquid medications on a routine and regular basis. A high intake of oral medications may constitute possible etiological

or aggravating factors for severe dental erosion^[4] and dental caries,^[5-7] as these preparations are acidogenic and cariogenic in nature.^[8,9] Many parents are aware that sugar causes tooth decay, but commonly compare this solely with the consumption of sweets and biscuits. They are often unaware of the hidden added sugar in many foods and drinks, including pediatric liquid medicines.^[10]

These pharmaceutical preparations have a greater sugar load, with a mean sugar content of 55%.^[11] Sugars are added in children's medicines primarily to mask the less pleasant taste of the active ingredients.^[12] Although added sugars and surplus acid ensures palatability of liquid preparations, they may produce unwanted dental side effects in children, who are already medically compromised.^[4]

Clinical observations linking long-term oral medication to rampant dental caries were performed since 1953,

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when James and Parfitt described the extensive labial caries that developed in children taking iron tonics.^[13] The most conclusive evidence was given by Roberts and Roberts^[9] and Feigal *et al.*,^[14] who showed that, continuous administration of sucrose-based medicines caused dental caries and related gingivitis. Rekola^[8] showed that syrups sweetened with sucrose or fructose or with a combination of fructose and sorbitol produced a marked and long-term drop in the plaque pH. A number of authors have expressed their concerns that oral liquid medications contribute to the total sugar load and to the development of dental caries in children.^[1,9,15]

In a previous part of this research we evaluated the acidogenic potential of commonly prescribed PLM. All the studied PLMs showed a different pattern of erosion of the primary enamel surface when viewed under scanning electron microscopy (SEM)^[16] and had calcium dissolution potential of the primary enamel.^[17] Hence, a step further was taken to determine the cariogenic potential of commonly prescribed pediatric liquid medicaments. This was studied by assessing the endogenous pH (i.e. the hydrogen-ion concentration), type and concentration of sugars present in them, and their effect on the growth of *S. mutans*.

MATERIALS AND METHODS

Eight commonly used PLMs were selected for the study. The PLMs included each of the two most commonly prescribed analgesics, antibiotics, antiasthmatic drugs, and nutritional supplements. The endogenous pH of the selected PLM was measured using a pH electrode meter [Table 1].^[18,19]

High Performance Liquid chromatography (HPLC) (Agilent 1100 system, UK) was used to analyze the type and concentration of sugars (sucrose and glucose) present in the PLM.^[19,20] Five milliliters of each PLM were pipetted into a 10 ml volumetric flask, to which 2 ml of diluent was added and sonicated for five minutes. Microdilutions of 1 ml were passed through a 0.45 µm filter paper and the supernatant was used for chromatography. All samples were prepared in triplicate.

The effect of the PLM on the *S. mutans* was assessed using the ditch plate method.^[21] Freeze-dried forms of the *S. mutans* MTCC 497 was obtained from the microbiological laboratory. After preparation of the inoculum, 1 ml of inoculum suspension was added to the sterilized Muller-Hilton agar medium and mixed thoroughly. About 20 ml was then dispensed into sterile petri dishes and allowed to solidify. Cylindrical cavities/wells were bored in the media after solidification using a sterile borer.

Two dilutions of each sample of PLM were prepared using sterile water to give 1:2 dilution (1 ml of sample + 1 ml of sterile water) and 1:10 dilution (1 ml of sample + 9 ml of sterile water). Each diluted sample of 0.1 ml was pipetted into the prepared wells on the agar plate. The plates were then kept at room temperature for two to four hours for preincubation diffusion. The plates were then incubated for 24 hours at 30 – 35°C, following which the plates were observed for zones of inhibition and/or exhibition. The maximum diameter of the zones was measured using a digital vernier calipers.

The data obtained were subjected to statistical analysis using the Mann–Whitney and Kruskal–Wallis tests and the SPSS software.

Table 1: Mean pH, concentration of sugars and growth of *Streptococcus mutans* due to pediatric liquid medicaments

PLM	Chemical composition	Brand name	pH of PLM	Concentration of sucrose and glucose (g%) (mean±SD)		Zone of inhibition and/or exhibition with <i>Streptococcus mutans</i> (mean±SD) (in mm)	
				Sucrose	Glucose	1:2 dilution	1:10 dilution
Analgesics	Nimuslide	Nise®	6.2±0.01*	8.09±0.03	0.74±0.01*	Nil	Nil
	Paracetomol	Crocina®	6.77±0.03	18.7±0.01*	1.21±0.01	Nil	Nil
Antibiotics	Amoxicillin	Mox®	6.62±0.03	12.50±0.05	0.00±0.00*	35.88±0.11 (inhibition)	28.16±0.02 (inhibition)
	Erythromycin	Althrocina®	6.73±0.04	0.07±0.00*	5.01±0.02	50.52±0.67 (inhibition)	45.64±0.18** (inhibition)
Antiasthmatics	Salbutamol	Salbid®	6.05±0.02*	8.19±0.06	0.89±0.02	Nil	Nil
	Theophylline	Theopid®	7.71±0.04	16.54±0.31	1.63±0.02	Nil	Nil
Multivitamin	Multivitamin	Vi-syneral®	6.67±0.04	7.13±0.06	6.13±0.03	Nil	Nil
	Multivitamin with Zinc	Zevit®	6.25±0.01	15.99±0.07	1.19±0.03	11.90±0.29 (exhibition)	12.67±0.10 (exhibition)

PLM = Pediatric liquid medicaments, SD = Standard deviation

RESULTS

The pH of the liquid medicaments ranged between 6.05 (Salbid®) and 6.77 (Crocina®), and were acidic, whereas, Theopid® had a basic pH of 7.71. Sucrose was observed in 7 PLM and glucose in 5 PLM. The highest concentration of sucrose was seen in Crocina®. The lowest concentration of sucrose was seen with Althrocin®, but it contained 5% of glucose. Mox® contained only sucrose. Zones of inhibition were seen with Mox® and Althrocin®, whereas, Zevit® showed zones of exhibition [Table 1].

DISCUSSION

The use of PLM is usually for a short duration, but for chronically ill children it may be a daily occurrence. The active ingredients in these medicines are necessary for improvement or maintenance of health; some inactive ingredients pose a risk to dental health.^[17] Children on long-term medication^[9,22] and who take medications very frequently due to coughs and common cold^[13,23] are under risk of developing dental caries, as these preparations are made palatable by adding sugars like sucrose, glucose or fructose in order to gain patient compliance. These readily fermentable carbohydrates in thick liquid preparations may add significantly to the dental caries potential in the young and chronically sick children. Hence, the purpose of this study was to assess the cariogenic potential of the commonly used PLM.

On an average, 60% of the population of developed countries take some form of medicine, of which about half are bought over-the-counter^[24] and 17% of children are given non-prescription cough medicine.^[1] Analgesics, cough medicines, and multivitamins are the commonly dispensed over-the-counter liquid preparations given to children.^[24,25] These observations formed the basis for the selection of PLM in our study.

Many liquid medications have an endogenous low pH^[26] that may itself contribute to demineralization or at least inhibit the demineralization–remineralization process in newly erupted teeth.^[27] The data sheet of the pediatric liquid medicaments used in the current study did not specify any valuable information about their pH or the specific kind of sucrose present. Along with the specific composition it read only as ‘sweetened with a particular flavor’. Therefore, the pH of each pediatric liquid medicament was measured using a pH electrode meter. The pH of the liquid medicaments ranged between 6.05 (Salbid®) and 6.77 (Crocina®), which were acidic, whereas Theopid® had a basic pH of 7.71.

The endogenous pH of a medication can be rapidly changed intraorally by salivary buffers. Alternatively, sugars metabolized by bacteria to acid end-products decrease the pH within an adherent bacterial-rich plaque that is relatively unavailable to salivary buffering. Low pH near the tooth surface causes ionic dissolution from the hydroxyapatite crystals and eventually carious lesions.^[28] An *in vivo* study has shown that PLM causes a drop in plaque pH that is sufficient to cause decalcification within 2–10 minutes following its initial exposure to the teeth.^[18]

Although pH is unquestionably important in the carious process, more researchers suggest that the sweeteners added to increase patient acceptance of tonics are more likely of primary importance to the development of rampant dental caries.^[9,13,14,19,23,28] Sugar is used as a vehicle for medicines and it is included in nearly all the formulations prepared, especially for children. The liquid preparations are usually sweetened with sucrose or glucose or fructose, and these are fermentable by the acidogenic bacteria in the mouth. Lokken *et al.*,^[15] and Imfeld^[6] suggested that the cariogenic potential present in medicines is due to the presence of sucrose and its availability to the oral plaque bacteria.

The amount of sucrose present in PLM varies from 0 to 67%.^[19,29] Concentrations of sucrose ranging from 11 to 86% were observed in 10 of 23 samples.^[19] An Indian study reported the presence of sugars in a range of 20.62 to 68.26% in PLM.^[30] Pomorico *et al.*,^[31] observed the presence of sucrose in seven of the ten samples studied, ranging between 5 and 54 g%. In our study, all the selected PLM showed the presence of at least one type of sugar and it varied from 0.74 to 18%.

Manufacturers are reluctant to omit sugars from formulations for fear of losing the several advantageous qualities it imparts, like: (1) it is a nontoxic sweetening agent; (2) free from after taste; and (3) acts as a preservative in the formulation. It remains widely used because it is cheap, easy to process, and available in a number of pure, dry, chemically and physically stable forms, with different particle sizes.^[12]

The presence of high concentrations of fermentable carbohydrates in medicated syrups may facilitate the growth of *S. mutans*, by rapidly metabolizing sugars to acids, thus initiating enamel demineralization. In our study, the growth of *S. mutans* was seen with Zevit®, a nutritional supplement. This may be due to the low pH and a higher content of sucrose in it. As it is a nutritional supplement it may contain constituents that can promote the growth of microorganisms. Also the presence of sodium selenite could have contributed to the promotion

of *S. mutans* growth.^[32] However, inhibition of the growth of *S. mutans* was seen with both the antibiotics studied. Our result was in accordance with the observations made by Subramaniam *et al.*, who observed a zone of inhibition with antibiotic syrups.^[33] Masters observed reduction in dental caries in children taking antibiotics for long time, but this effect disappeared after four years of age.^[34] A significant decline in dental caries with the use of antibacterial syrup medication was also observed by other researchers.^[35] Although antibiotics are antimicrobial in nature, their use in children who are on long-term medication should not be ignored, as these preparations have an enamel-erosive potential.^[16,17] Also the presence of sugars as sweetening agent in these preparations should be a concern for the prescribing practitioners. Other medicaments studied did not promote or inhibit *S. mutans* growth. However, their endogenous pH has been seen to have an acidogenic potential,^[16,17] hence, caution must be taken during prescribing these PLM.

Primary teeth are known to be less mineralized than permanent teeth, and particularly as the enamel surface of deciduous teeth is not as mature as that of permanent teeth, it is more liable to dental caries.^[36] Added to this, most of the syrups are given in two to three divided doses — the night dose, especially, has a deleterious effect on the enamel due to the following reasons: (1) Although saliva is the key defense mechanism against demineralization, at night, its flow rate is diminished.^[37] Some medications, such as anticonvulsants, sedatives or antihistamines also lower the salivary flow.^[38] (2) In young children, the oral clearance process can be expected to be less effective than in adults, due to lower salivary flow and less pronounced oral muscular coordination ability.^[37] (3) Lack of the fully developed interest and ability to eliminate particles retained in the mouth after food/liquid intake.^[39]

As this study was induced under *in vitro* conditions, it is clear that the results are not completely transferable to the *in vivo* situation. The presence of the pellicle will protect the teeth from acidic challenges. It has also been suggested that the amount and quality of saliva, in particular its buffering capacity, are important in the occurrence of dental caries. Other factors present in the oral environment like retention, bacterial activity, sugar formation, oral hygiene, and hormone factors may have a significant contributory effect for causation of dental caries, along with the prescribed medicaments.

CONCLUSIONS

1. The pH of the liquid medicaments ranged between 6.05 (Salbid®) and 7.71(Theopid®)

2. Sucrose was observed in 7 PLM and glucose in 5 PLM. The highest and lowest concentration of sucrose was seen in Crocin® (19.80 g%) and Althrocin®, respectively
3. Both the antibiotic PLM inhibited the *S. mutans* growth
4. Zevit promoted the growth of *S. mutans* growth.

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